

DOCUMENT-IDENTIFIER: US 20040192590 A1

TITLE: Method of using lectins for contraception, prophylaxis against diseases transmittable by sexual contact, and therapy of such diseases, and apparatus for administering lectins

Detail Description Paragraph:

[0047] The lectins may be administered in any fluid or ointment vehicle suitable for topical administration of pharmaceutical compounds. Thus, creams, ointments, foams, suppositories, ovules and the like may be formulated in which the selected lectins are dispersed in a non-toxic vehicle suitable for topical and in particular for vaginal administration. Such vehicles include white petrolatum, hydrophilic petrolatum, lanolin emulsions, polyethylene glycols, cocoa butter and the like. Useful vehicles include emollient oils such as water-soluble oils, e.g., liquid polyethylene glycols, which promote complete and uniform distribution of the medicament within the vagina. Representative suitable vehicles include a lubricating jelly comprised of water, propylene glycol, hydroxyethyl cellulose, benzoic acid and sodium hydroxide, a water-soluble oil comprised of water, glycerin, propylene glycol, polyquaternium #5, methyl paraben and propyl paraben; a cream comprised of benzyl alcohol, cetaryl alcohol, cetyl esters wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate; and a suppository comprised of polyethylene glycol (PEG) 8, PEG-32, PEG-20 stearate, benzethonium chloride, methyl paraben and lactic acid.

DOCUMENT-IDENTIFIER: US 5872126 A

TITLE: Methods and compositions for treating preterm labor

Brief Summary Text (675):

Formulations for vaginal administration may be presented as a ~~vaginal suppository with a conventional carrier, i.e., a base~~ that is nontoxic and nonirritating to the vaginal membranes, compatible with the 5.alpha.-reductase type 1 inhibitors, and is stable in storage and does not bind or interfere with the release of the 5.alpha.-reductase type 1 inhibitor. Suitable bases include: cocoa butter (theobroma oil), polyethylene glycols (such as carbowax and polyglycols), glycol-surfactant combinations, polyoxyl 40 stearate, polyoxyethylene sorbitan fatty acid esters (such as Tween, Myrj, and Arlacel), glycerinated gelatin, and hydrogenated vegetable oils. When glycerinated gelatin suppositories are used, a preservative such as methylparaben or propylparaben may be employed. For vaginal administration, glycerinated gelatin is the preferred base. Other formulations appropriate for vaginal administration include creams, jellies and aerosol foams.

DOCUMENT-IDENTIFIER: US 6645974 B2

TITLE: Androgen receptor modulators and methods for use thereof

Brief Summary Text (111):

Formulations for vaginal or rectal administration may be presented as a suppository with a conventional carrier, i.e., a base that is nontoxic and nonirritating to mucous membranes, compatible with the compound of structural formula I, and is stable in storage and does not bind or interfere with the release of the compound of structural formula I. Suitable bases include: cocoa butter (theobroma oil), polyethylene glycols (such as carbowax and polyglycols), glycol-surfactant combinations, polyoxyl 40 stearate, polyoxyethylene sorbitan fatty acid esters (such as Tween, Myrj, and Arlacel), glycerinated gelatin, and hydrogenated vegetable oils. When glycerinated gelatin suppositories are used, a preservative such as methylparaben or propylparaben may be employed.

WEST Search History

DATE: Wednesday, June 22, 2005

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		<i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND</i>	
<input type="checkbox"/>	L1	(intravaginal\$ or vagina\$).ti. and vaccin\$.ti.	9
<input type="checkbox"/>	L2	(intravaginal\$ or vagina\$ or intragential\$ or genital\$ or urogenital\$ or intraurethra\$).ti. and vaccin\$.ti.	20
<input type="checkbox"/>	L3	l2 and (\$suppository or \$suppositories or suppositor\$ or depot or delivery)	5

END OF SEARCH HISTORY

YSTEM:OS - DIALOG OneSearch

File 155:MEDLINE(R) 1951-2005/Jun W3

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File 654:US Pat.Full. 1976-2005/Jun 21

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File 348:EUROPEAN PATENTS 1978-2005/Jun W02

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File 5:Biosis Previews(R) 1969-2005/Jun W2

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File 160:Gale Group PROMT(R) 1972-1989

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File 340:CLAIMS(R)/US Patent 1950-05/Jun 21

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Set Items Description

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Cost is in DialUnits

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Terminal set to DLINK

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Set Items Description

S1 84 ((VAGINA? OR GENITAL? OR UROGENITAL? OR INTRAVAGIN?) (5N) -
VACCIN?) (100N) SUPPOSITOR?

S2 77 RD (unique items)

00504736

RECOMBINANT CtB-BASED VACCINES

VACCINS RECOMBINES A PARTIR DE LA SOUS-UNITE B DE LA TOXINE CHOLERIQUE

Patent Applicant/Assignee:

MAXIM PHARMACEUTICALS INC,

Inventor(s):

EWALT Karla L,

HANDLEY Harold H Jr,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9936088 A1 19990722

Application: WO 99US943 19990115 (PCT/WO US9900943)

Priority Application: US 9871607 19980116

Designated States:

(Protection type is "patent" unless otherwise stated - for applications prior to 2004)

AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH
GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN
MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK
ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE
SN TD TG

Publication Language: English

Fulltext Word Count: 19500

00970290

MUTANT PROTEINS, HIGH POTENCY INHIBITORY ANTIBODIES AND FIMCH CRYSTAL
STRUCTURE

PROTEINES MUTANTES, ANTICORPS A FORT POUVOIR INHIBITEUR ET STRUCTURE
CRISTALLINE FIMCH

Patent Applicant/Assignee:

MEDIMMUNE INC, 35 West Watkins Mill Road, Gaithersburg, MD 20878, US, US
(Residence), US (Nationality)

Inventor(s):

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HUNG Chia-Suei, 1425 Cutter Avenue, St. Louis, MO 63139, US,

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Legal Representative:

POISSANT Brian M (et al) (agent), Pennie & Edmonds LLP, 1155 Avenue of
the Americas, New York, NY 10036, US,

Patent and Priority Information (Country, Number, Date):

Patent: WO 2002102974 A2-A3 20021227 (WO 02102974)

Application: WO 2001US47994 20011210 (PCT/WO US0147994)

Priority Application: US 2000254353 20001208; US 2001301878 20010629

Designated States:

(Protection type is "patent" unless otherwise stated - for applications
prior to 2004)

AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ
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SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR

(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

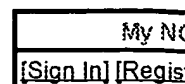
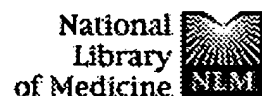
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English

Filing Language: English

Fulltext Word Count: 990996



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☐ 1: J Tradit Chin Med. 1996 Jun;16(2):151-6.

[Related Articles, Links](#)

Advances in treatment of ano-rectal diseases by the anal suppository method.

Yang X, Wang J, Xie R.

PLA 520 Hospital, Mianyang, Sichuan Province.

Publication Types:

- Review
- Review, Tutorial

PMID: 9389147 [PubMed - indexed for MEDLINE]

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Jun 6 2005 07:23:23

Scand J Immunol. 1996 Oct;44(4):408-14.

[Related Articles, Links](#)

Local intravaginal vaccination of the female genital tract.

Wassen L, Schon K, Holmgren J, Jertborn M, Lycke N.

Department of Gynecology & Obstetrics, University of Goteburg, Sweden.

In a clinical trial the authors tested whether local intravaginal or oral vaccination would stimulate a mucosal immune response in the female genital tract. The whole cell/B subunit (CTB) oral cholera vaccine was used. Two groups of previously unimmunized volunteers were given three doses of vaccine at 2-week intervals: a first group of seven women received oral immunizations and a second group of seven women were immunized locally in the genital tract by mixing the vaccine with a well defined gel, eldexomer, and applying it directly in the fornix of the vagina. The women were given the first vaccination on day 10 of the menstrual cycle. Sampling of peripheral blood and of cervical mucus (CM) using an Aspiplaire syringe was performed immediately prior to the first dose and at 8-10 days following the last immunization. The study showed that while only three of the seven orally immunized women responded with detectable IgA and IgG anti-CTB antibodies in the genital tract, six out of the seven women in the locally vaccinated group responded with genital tract antibodies. The responses were also generally stronger and CM contained higher specific IgA and secretory component containing anti-CTB titres in the locally vaccinated group. Of the orally vaccinated individuals all responded with increases in serum anti-CTB IgG and 4/7 also exhibited specific IgA serum titres. By contrast, only 3/7 in the intravaginal group responded with increases in serum IgG and IgA anti-CTB titers following immunization. The authors conclude that local intravaginal vaccination using a well-defined gel appears to be the route of choice to stimulate immunity in the female genital tract.

Publication Types:

- Clinical Trial
- Controlled Clinical Trial

J Urol. 1997 Jun;157(6):2049-52.

[Related Articles, Links](#)

Vaginal mucosal immunization for recurrent urinary tract infection: phase II clinical trial.

Uehling DT, Hopkins WJ, Balish E, Xing Y, Heisey DM.

Department of Surgery, University of Wisconsin, Madison, USA.

PURPOSE: Decreased local immunity to uropathogenic bacteria may be a factor predisposing women to recurrent urinary tract infections. Our phase I study demonstrated the safety of a multi-strain vaccine administered as a vaginal suppository. A phase II study was conducted to determine vaccine efficacy. **MATERIALS AND METHODS:** A total of 91 women susceptible to recurrent urinary tract infections was entered into the study and the courses were analyzed in a randomized, double-blind, placebo controlled trial of vaginal mucosal immunization. Subjects received 3 vaginal suppositories at weekly intervals. Depending on the treatment group each suppository contained 1 of 2 vaccine doses or suppository material only. Each patient was followed for 5 months to record infection episodes, and obtain urine, vaginal irrigates and serum to measure immunological responses. **RESULTS:** Immunogen treated women who were off antibiotic prophylaxis throughout the study had a significant delay in interval to reinfection during the first 8 weeks compared to women receiving placebo. Mean interval until reinfection was delayed from 8.7 weeks for placebo treated to 13 weeks for vaccine treated women. Immunological responses in serum, urine and vaginal fluid were variable. No serious adverse effects were observed. **CONCLUSIONS:** These data demonstrate that vaginal mucosal immunization can enhance resistance to urinary tract infections in susceptible patients.

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11873468 PMID: 9146577

Vaginal mucosal immunization for recurrent urinary tract infection: phase II clinical trial.

Uehling D T; Hopkins W J; Balish E; Xing Y; Heisey D M

Department of Surgery, University of Wisconsin, Madison, USA.

Journal of urology (UNITED STATES) Jun 1997, 157 (6) p2049-52,

ISSN 0022-5347 Journal Code: 0376374

Contract/Grant No.: DK 30808; DK; NIDDK

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Main Citation Owner: NLM

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PURPOSE: Decreased local immunity to uropathogenic bacteria may be a factor predisposing women to recurrent urinary tract infections. Our phase I study demonstrated the safety of a multi-strain **vaccine** administered as a **vaginal suppository**. A phase II study was conducted to determine vaccine efficacy. **MATERIALS AND METHODS:** A total of 91 women susceptible to recurrent urinary tract infections was entered into the study and the courses were analyzed in a randomized, double-blind, placebo controlled trial of vaginal mucosal immunization. Subjects received 3 vaginal **suppositories** at weekly intervals. Depending on the treatment group each **suppository** contained 1 of 2 vaccine doses or **suppository** material only. Each patient was followed for 5 months to record infection episodes, and obtain urine, vaginal irrigates and serum to measure immunological responses. **RESULTS:** Immunogen treated women who were off antibiotic prophylaxis throughout the study had a significant delay in interval to reinfection during the first 8 weeks compared to women receiving placebo. Mean interval until reinfection was delayed from 8.7 weeks for placebo treated to 13 weeks for vaccine treated women. Immunological responses in serum, urine and vaginal fluid were variable. No serious adverse effects were observed. **CONCLUSIONS:** These data demonstrate that vaginal mucosal immunization can enhance resistance to urinary tract infections in susceptible patients.

Tags: Female; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Adjuvants, Immunologic--administration and dosage--AD; *Bacterial Vaccines--administration and dosage--AD; *Urinary Tract Infections--therapy--TH; Administration, Intravaginal; Adolescent; Adult; Aged; Aged, 80 and over; Double-Blind Method; Humans; Middle Aged; Recurrence

CAS Registry No.: 0 (Adjuvants, Immunologic); 0 (Bacterial Vaccines); 0 (SolcoUrovac)

Record Date Created: 19970610

Record Date Completed: 19970610

04409174 Supplier Number: 46468818 (THIS IS THE FULLTEXT)
**Urinary Tract Infections (Vaccines) Early Results Suggest Vaginal
Immunization May Delay Recurrent UTIs**

Infectious Disease Weekly, pN/A

June 17, 1996

ISSN: 1078-2850

Language: English Record Type: Fulltext

Document Type: Newsletter; Professional Trade

Word Count: 243

TEXT:

Early results of a Phase II clinical trial of vaginal immunization against recurrent urinary tract infections (RUTI) yield promising results.

Despite no identifiable anatomic abnormalities, many women remain highly susceptible to RUTI. Because mucosal immunity can boost host defenses against infection, David T. Uehling et al. attempted to boost mucosal immunity against RUTI in the bladder through vaginal immunization.

Uehling presented results of this research to the 91st Annual Meeting of the American Urological Association, held May 4-9, 1996, in Orlando, Florida (Abstract: "Early Results of Phase II Clinical Trial of Vaginal Immunization for RUTI").

In the previous Phase I clinical trial of this protocol (J. Urol., 1994;152:2308-2311), only minimal adverse reactions were noted. Seventy-five women were randomized to receive either the vaccine or placebo in the Phase II trial. The **vaccine** group received **vaginal suppositories** containing either one or two ampules of a multi-strain vaccine. Both groups were followed for infection incidence and immunologic responses for 20 weeks.

After the women were removed from prophylactic treatment, five of nine women (56 percent) in the placebo group had a UTI within the first 28 days, while only two of 24 (9 percent) had a UTI in the vaccine group.

No differences were found in infection rates and in urine and vaginal immunoglobulin levels between the groups as the study progressed.

"In susceptible women, vaginal immunization may delay the interval between re-infections," concluded Uehling et al. at the conference. - by Michelle Marble

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PUBLISHER NAME: Charles W. Henderson

EVENT NAMES: *310 (Science & research)

GEOGRAPHIC NAMES: *1USA (United States)

PRODUCT NAMES: *8000292 (Gynecological R&D); 2831210 (Vaccines for Human Use)

INDUSTRY NAMES: BUSN (Any type of business); HLTH (Healthcare - Medical and Health)

NAICS CODES: 54171 (Research and Development in the Physical, Engineering, and Life Sciences); 325412 (Pharmaceutical Preparation Manufacturing)

0429677 **Image available**

SECRETORY IMMUNOGLOBULIN A AS A MUCOSAL VACCINE DELIVERY SYSTEM
IMMUNOGLOBULINE A (IgA) SECRETOIRE UTILISEE COMME SYSTEME D'ADMINISTRATION
DE VACCIN PAR VOIES MUQUEUSES

Patent Applicant/Assignee:

INSTITUT SUISSE DE RECHERCHES EXPERIMENTALES SUR LE CANCER ISREC,
KRAEHENBUHL Jean-Pierre,
CORTHESEY Blaise,
KAUFMANN Muriel,
PEITSCH Manuel,

Inventor(s):

KRAEHENBUHL Jean-Pierre,
CORTHESEY Blaise,
KAUFMANN Muriel,
PEITSCH Manuel,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9820141 A1 19980514
Application: WO 97EP5947 19971028 (PCT/WO EP9705947)
Priority Application: GB 96203051 19961101

Designated States:

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AL AU BA BB BG BR CA CN CU CZ EE GE HU IL IS JP KE KP KR LC LK LR LT LV
MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA US UZ VN YU GH KE LS MW SD
SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT
LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 11648

Fulltext Availability:

Detailed Description

Detailed Description

... applied as a dry powder in the form of a spray, e. g. nasal spray.
Suppositories or ointment are useful for rectal or vaginal application.
Conventional production methods are applied making...

...of effective amounts of the pathogen-specific sIgA carrying the foreign chimeric epitope. The pharmaceutical **vaccine** is administered nasally, **genitally**, rectally or preferably orally for those pathogens that infect mucosal surfaces of the respiratory, urogenital...

...are used when nasal administration is required, e.g. in the case of respiratory infections. **Suppositories** or ointment are applied in case of rectal or vaginal infections.

The pharmaceutical preparations have...

00362511

CLOSTRIDIUM DIFFICILE TOXINS AS MUCOSAL ADJUVANTS

TOXINES DE CLOSTRIDIUM DIFFICILE UTILISEES COMME ADJUVANTS AGISSANT SUR LES MUQUEUSES

Patent Applicant/Assignee:

ORAVAX INC,

Inventor(s):

THOMAS William D Jr,

MONATH Thomas P,

ZHANG Zhenxi,

TORRES-LOPEZ Francisco Javier,

LEI Wende,

LYERLY David M,

MONCRIEF James S,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9702836 A1 19970130

Application: WO 96US11142 19960701 (PCT/WO US9611142)

Priority Application: US 95499384 19950707; US 95543708 19951016

Designated States:

(Protection type is "patent" unless otherwise stated - for applications prior to 2004)

AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP
KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD
SE SG SI SK TJ TM TR TT UA UG UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD
RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG
CI CM GA GN ML MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 7686

Fulltext Availability:

Detailed Description

Detailed Description

... e.g., phosphate-buffered saline), a bicarbonate solution (e.g., 0,24 M NaHCO₃), a **suppository**, cream, or jelly), which are selected on the basis of the mode and route of...

...Industrial

Pharmacy, 2nd edn., Lea & Febiger, Philadelphia PA, 1976), In the case of rectal and **vaginal** administration, the **vaccines** are administered using methods and carriers 15 standardly used in administering pharmaceutical materials to these regions, For example, **suppositories**, creams (e.g., cocoa butter), or jellies, as well as standard vaginal applicators, droppers, syringes...

00362485 **Image available**

POLYMERIC LAMELLAR SUBSTRATE PARTICLES FOR DRUG DELIVERY

**PARTICULES POLYMERES LAMELLAIRES DE SUBSTRAT POUR L'ADMINISTRATION DE
MEDICAMENT**

Patent Applicant/Assignee:

THE UNIVERSITY OF NOTTINGHAM,
COOMBES Allan Gerald Arthur,
DAVIS Stanley Stewart,
MAJOR Diane Lisa,
WOOD John Michael,

Inventor(s):

COOMBES Allan Gerald Arthur,
DAVIS Stanley Stewart,
MAJOR Diane Lisa,
WOOD John Michael,

Patent and Priority Information (Country, Number, Date):

Patent: WO 9702810 A2 19970130
Application: WO 96GB1695 19960715 (PCT/WO GB9601695)
Priority Application: GB 9514285 19950713

Designated States:

(Protection type is "patent" unless otherwise stated - for applications
prior to 2004)

AU CA GB JP NO US AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

Publication Language: English

Fulltext Word Count: 6002

Fulltext Availability:

Detailed Description

Detailed Description

... be used to coat the dosage form. Vaginal systems suitable for
delivery include gels and **vaginal Suppositories** . Rectally
administrated
vaccines can be given as enemas or incorporated into **suppositories** .

The invention further provides a method of making composition according
to Claim 1 to 12...

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cyclosporin

<drug> Cyclic undecapeptide isolated from Tolypocladium inflatum, that has potent immunosuppressant activity on both humoral and cellular systems.

The use of cyclosporin has made transplant surgery much easier, although the long term consequences of suppressing immune function are not yet clear.

Used widely as an an antirejection drug in transplant surgery and to prevent and treat rejection and graft-versus-host disease in bone marrow transplant patients by suppressing their normal immune system.

(13 Nov 1997)

Previous: cyclopropane synthetase, cyclops, cycloserine, cyclosis, Cyclospora, cyclospora cayetanensis

Next: cyclosporin A, cyclosporin A synthetase, cyclosporine, cyclosporins

Published at the Centre for Cancer Education, University of Newcastle upon Tyne

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cyclosporin

/siklosporin/ (also cyclosporine)

• **noun** a drug used to prevent the rejection of grafts and transplants.

— ORIGIN from Latin *spora* 'spore' (because it is produced from a fungus).

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⑫

EUROPEAN PATENT APPLICATION

⑰ Application number: 89313499.9

⑮ Int. Cl.⁵: **G01N 33/68, G01N 33/58,**
G01N 33/548

⑱ Date of filing: 22.12.89

⑳ Priority: 23.12.88 US 288912

㉑ Date of publication of application:
27.06.90 Bulletin 90/26

㉒ Designated Contracting States:
CH DE FR GB IT LI NL SE

㉓ Applicant: **E.I. DU PONT DE NEMOURS AND**
COMPANY
1007 Market Street
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Inventor: Miller, Warren Keene
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㉕ Representative: Myerscough, Philip Boyd et al
J.A.Kemp & Co. 14, South Square Gray's Inn
London, WC1R 5EU(GB)

㉖ **Enzyme-linked immunoassay for measurement of cyclosporin A levels in whole blood samples.**

㉗ An enzyme-linked immunoassay for the determination of cyclosporin A levels in whole blood samples is provided based on the utilization of β -D-galactosidase as an enzyme label and chlorophenol red- β -D-galactopyranoside or resorufin- β -D-galactopyranoside as a β -D-galactosidase substrate.

EP 0 375 454 A1

ENZYME-LINKED IMMUNOASSAY FOR MEASUREMENT OF CYCLOSPORIN A LEVELS IN WHOLE BLOOD SAMPLES

TECHNICAL FIELD

This invention relates to the measurement of cyclosporin A levels in whole blood samples.

5

BACKGROUND ART

10 Cyclosporin A is a potent immunosuppressive agent which has been successful in prolonging the survival of kidney, liver and heart allogeneic transplants in humans. Cyclosporin A has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection and delayed hypersensitivity. Other cyclosporins, such as cyclosporin G, have also been used as immunosuppressive agents, but are not as widely used as cyclosporin A. High doses of cyclosporin A can
15 cause hepatotoxicity and nephrotoxicity and low doses can lead to possible organ rejection. For these reasons, patients receiving cyclosporin A should be monitored at repeated intervals for cyclosporin A blood levels and subsequent dose adjustments should be made.

In blood, cyclosporin A partitions into red blood cells. Partitioning of cyclosporin A increases as the temperature of blood decreases from body temperature to room temperature. Therefore, to eliminate
20 analytical variability due to time and temperature equilibration, it is advantageous to perform determinations of cyclosporin A blood levels on whole blood samples. Currently, cyclosporin A levels in whole blood samples are determined using radioimmunoassays and high performance liquid chromatography (HPLC). Radioimmunoassays are less advantageous than other immunoassays, such as enzyme-linked immunoassays, because radioimmunoassays require the use of a radioisotope which poses numerous problems
25 associated with handling, storage, and disposal. HPLC is less advantageous than other assays because it requires laborious procedures, such as solvent extraction of cyclosporin A. There have been no cyclosporin A non-radiometric immunoassays described which can be performed directly on whole blood samples.

Enzyme-linked immunoassays have achieved widespread use for the measurement of clinically important analytes. There are many different types of enzyme-linked immunoassays, such as sandwich im-
30 munoassays and competitive and noncompetitive heterogeneous immunoassays. Enzyme-linked immunoassays often utilize an enzyme-labeled antibody specific for the analyte of interest. The enzyme-labeled antibody binds to an analyte of interest in a sample and the enzymatic activity of either the bound enzyme-labeled antibody or the free enzyme-labeled antibody is measured by reacting the enzyme with a substrate to produce a detectable chromophore. Affinity columns containing immobilized analyte are often used to
35 separate the free labeled antibody from the bound labeled antibody so that the enzymatic activity of the bound labeled antibody can be measured. Virtually any enzyme that can be coupled to an antibody and can react with a substrate to produce a detectable chromophore can be used in enzyme-linked immunoassays.

An enzyme-linked immunoassay which is to be performed on whole blood samples has unique requirements for selection of enzyme label and enzyme substrate. Since a whole blood sample can contain
40 lysed red blood cells, an enzyme label used in an enzyme-linked immunoassay performed on whole blood samples cannot be endogenous to red blood cells. The enzyme β -D-galactosidase is not endogenous to red blood cells and is a suitable enzyme label for an enzyme-linked immunoassay performed on whole blood samples.

Red blood cells contain heme, which has an intense absorption peak at 405 nm, known as the Soret
45 band. The absorbance peak at 405 nm is so intense that the measurement of absorbance of a 10 μ L whole blood sample diluted 500-fold would be beyond the capacity of a conventional spectrophotometer. Therefore, a suitable β -D-galactosidase substrate for use in an enzyme-linked immunoassay performed on whole blood samples should produce a chromophore which does not absorb at or near 405 nm since the interference from the Soret band would be too great. A β -D-galactosidase substrate most commonly used in
50 enzyme-linked immunoassays is o-nitrophenyl- β -D-galactopyranoside (ONPG). However, since ONPG produces a chromophore which absorbs at 405 nm, it is not a suitable β -D-galactosidase substrate for use in an enzyme-linked immunoassay performed on whole blood samples.

Two classes of β -D-galactosidase substrates producing chromophores which absorb in the visible range, approximately 560 nm to 590 nm, are phenolsulphonphthaleinyl- β -D-galactosides (U.S. Patent

4,886,622, issued May 26, 1987, to Kuhr et al.) and glycosides of resorufin derivatives (DE 3411574, issued October 3, 1985). These substrates are described as being useful for enzyme immunoassays in which β -D-galactosidase is used as an indicator enzyme. While no interference in absorbance measurement would be caused by the Soret band, oxyhemoglobin, another constituent of red blood cells, has an absorbance peak at 577 nm. Therefore, the two above-identified classes of β -D-galactosidase substrates are not expected to be suitable for an enzyme-linked immunoassay performed on whole blood samples because of interference from oxyhemoglobin.

There remains a need for an enzyme-linked immunoassay for the direct and rapid measurement of cyclosporin A levels in whole blood samples.

SUMMARY OF THE INVENTION

The enzyme-linked immunoassay of this invention for the measurement of cyclosporin A levels in whole blood samples comprises the steps of:

- (a) lysing red blood cells in a sample of whole blood containing cyclosporin A;
- (b) contacting the lysed whole blood sample with excess β -D-galactosidase-labeled anti-cyclosporin antibody to form a labeled antibody-cyclosporin A complex;
- (c) separating unbound antibody from the complex by contacting the mixture formed in step (b) with a solid phase comprising cyclosporin immobilized on a solid support; and
- (d) determining the amount of the β -D-galactosidase label in the complex as a measure of cyclosporin A by adding a β -D-galactosidase substrate selected from the group consisting of chlorophenol red- β -D-galactopyranoside and resorufin- β -D-galactopyranoside.

DESCRIPTION OF THE INVENTION

The enzyme-linked immunoassay of this invention is useful for measuring cyclosporin A levels in whole blood samples of patients receiving cyclosporin A. Monitoring of cyclosporin A blood levels and subsequent cyclosporin A dosage adjustment are necessary to prevent toxic effects caused by high cyclosporin A blood levels and to prevent organ rejection caused by low cyclosporin A blood levels.

Unexpectedly, it has been found that an enzyme-linked immunoassay for measurement of cyclosporin A in whole blood samples can be performed by using β -D-galactosidase as an enzyme label and chlorophenol red- β -D-galactopyranoside (CPRG) or resorufin- β -D-galactopyranoside (ReG) as a β -D-galactosidase substrate. These two substrates have been found to have sensitivities so high that the volume of whole blood used as a sample in the immunoassay can be greatly reduced while still maintaining acceptable precision and accuracy. Therefore, even though these substrates produce chromophores which absorb at the same wavelength as oxyhemoglobin, the sample volume can be made to be sufficiently small to minimize oxyhemoglobin absorbance interference.

CPRG and ReG are disclosed among the numerous β -D-galactosidase substrates in U.S. 4,668,622 and DE 3411574. It is believed, however, that the other β -D-galactosidase substrates disclosed in the two above-identified patents are not as sensitive as CPRG and ReG and, therefore, an enzyme-linked immunoassay for use on whole blood samples utilizing such substrates can require a larger whole blood sample volume. Since a larger sample volume results in higher absorbance interference from oxyhemoglobin, the immunoassay cannot be performed accurately without a means for reducing such absorbance interference. One means for reducing the absorbance interference is to include potassium ferricyanide in the immunoassay to convert oxyhemoglobin to methemoglobin, which has a low, broad absorbance peak between 550 and 600 nm. The advantage of using CPRG or ReG as β -D-galactosidase substrates in the enzyme-linked immunoassay of this invention is that there is no need for the use of potassium ferricyanide since both substrates are sufficiently sensitive to allow the use of small sample volumes.

The enzyme-linked immunoassay of the present invention is performed by contacting a lysed whole blood sample containing cyclosporin A with excess β -D-galactosidase-labeled anti-cyclosporin antibody to form a reaction mixture containing a complex of cyclosporin A with labeled antibody and free labeled antibody, separating free antibody from the reaction mixture by contacting the reaction mixture with a solid phase comprising an immobilized cyclosporin on a solid support, separating the solid phase from the liquid

phase, and measuring the amount of the bound β -D-galactosidase label in the liquid phase by adding to the liquid phase CPRG or ReG as a β -D-galactosidase substrate.

Specifically, the red blood cells of a whole blood sample containing cyclosporin A must be lysed to release cyclosporin A. Red blood cell-lysis can be accomplished by many methods, such as sonication, detergent lysis and distilled water lysis. The lytic agent chosen should be compatible with the β -D-galactosidase-labeled anti-cyclosporin antibody. Although some detergents can denature β -D-galactosidase, it has been found that by using CPRG and ReG as β -D-galactosidase substrates, the sample volume can be made to be sufficiently small to minimize the denaturing effect of the detergent. The preferred lysis method uses distilled water.

After lysis, a reaction mixture is formed by contacting the lysed whole blood sample with excess β -D-galactosidase-labeled anti-cyclosporin antibody and incubating the reaction mixture for a time and at a temperature sufficient to permit the labeled antibody to form a complex with all of the cyclosporin A in the sample. This usually takes 10 - 30 minutes at room temperature. Anti-cyclosporin antibody can be obtained commercially or prepared by known methods. The anti-cyclosporin antibody can be polyclonal or monoclonal. A monoclonal anti-cyclosporin antibody specific for cyclosporin A is preferred. The anti-cyclosporin antibody is labeled with β -D-galactosidase by standard conjugation techniques.

The unbound β -D-galactosidase-labeled anti-cyclosporin antibody is separated from the reaction mixture by contacting the reaction mixture with a solid phase comprising cyclosporin immobilized on a solid support for a time sufficient to permit the unbound labeled antibody to form a complex with the immobilized cyclosporin. This usually occurs in approximately one minute. Any cyclosporin which can be immobilized on a solid support can be utilized in the enzyme-linked immunoassay of the present invention so long as such cyclosporin is capable of forming a complex with the anti-cyclosporin antibody. Cyclosporin C is preferred for the ease with which it can be immobilized on a solid support.

The immobilization of cyclosporin can be accomplished by a number of known immobilization techniques. The preferred immobilization technique for cyclosporin C is to derivatize cyclosporin C to cyclosporin C-hemisuccinate and couple it to a protein, such as albumin or globulin, which can be covalently coupled to a solid support.

Cyclosporin can be immobilized on a variety of solid supports. The solid support is chosen for its flow characteristics and can include beaded dextran, beaded agarose, polyacrylamide, or glass. A preferred solid support useful in the enzyme-linked immunoassay of this invention is described in applicants' assignee's, E. I. du Pont de Nemours and Company, copending patent application S.N. 07/074,242, filed July 16, 1987, incorporated herein by reference.

The preferred solid support comprises a beaded dextran chromatographic column containing an immobilized flocculating agent and trapped stabilized chromium dioxide particles having cyclosporin bound to their surfaces. Any flocculating agent can be used, but polyethyleneimine (PEI) is preferred. PEI can be attached to beaded dextran having a diameter of approximately 40 to 120 microns, such as Sephadex G-10 resin, by simple adsorption. This can be accomplished by soaking Sephadex G-10 resin in a 1% solution of PEI in a 0.15M sodium phosphate buffer.

The stabilized chromium dioxide particles useful in the preferred solid support are those described in U.S. Patent 4,661,408, issued April 28, 1987, incorporated herein by reference. These particles consist of a core of rutile chromium dioxide which has been extensively surface reduced, coated with alumina, further coated with silica containing borate and still further coated with a silane to which is attached cyclosporin. These particles have large surface areas, 40-100 m²/g, are stable in aqueous solution and can be readily coupled to cyclosporin. The particles coupled to cyclosporin are eluted through the beaded dextran chromatographic column containing immobilized flocculating agent and become trapped within the column. It has been found that by using the preferred solid support in the enzyme-linked immunoassay of this invention, the amount of cyclosporin required to remove unbound labeled anti-cyclosporin antibody is reduced by over 300-fold compared to the amount required when using beaded dextran alone as a solid support.

The solid phase is separated from the liquid phase by standard separation techniques. The preferred separation technique is to elute the liquid phase through the preferred solid support described above.

The amount of cyclosporin A is determined by measuring the amount of the bound β -D-galactosidase label in the liquid phase. The amount of bound β -D-galactosidase is determined by adding to the liquid phase either CPRG or ReG as a β -D-galactosidase substrate and measuring spectrophotometrically the amount of chromophore produced at 577 nm.

The enzyme-linked immunoassay of this invention can be performed manually or it can be adapted to a variety of automated or semi-automated instrumentation, such as the aca® discrete clinical analyzer (a registered trademark of E. I. du Pont de Nemours and Company, Inc., Wilmington, De). In performing the

assay on an aca® analyzer, a whole blood sample is first lysed and preincubated with excess β -D-galactosidase-labeled anti-cyclosporin antibody outside the instrument. A known volume of this mixture is automatically injected into an analytical test pack (described in U.S. Patent Re. 29,725 to Johnson et al., reissued August 8, 1978, and incorporated herein by reference) in the filling station of the instrument, followed by a volume of buffer sufficient to bring the final in-pack volume to approximately 5mL. The sample mixture percolates through a column of cyclosporin immobilized on a porous support located in the pack header and is eluted directly into the pack. The eluted fraction contains β -D-galactosidase-labeled anti-cyclosporin antibody complexed with cyclosporin A from the whole blood sample. The pack is automatically processed at 37 °C with the addition of CPRG or ReG immediately preceding the absorbance measurements at 577nm.

EXAMPLE

MEASUREMENT OF CYCLOSPORIN A IN WHOLE BLOOD SAMPLES

A. IMMOBILIZATION OF CYCLOSPORIN ON SOLID SUPPORT

Two hundred and fifty mg of cyclosporin C (Sandoz Ltd.), 144 mg of 4-dimethylaminopyridine and 70 mg of succinic anhydride were mixed in 0.8 mL of anhydrous pyridine. This mixture was heated at approximately 75 °C for 4 hours and approximately 30 mL of methylene chloride was then added to the mixture. The resulting mixture was washed three times with 15 mL of 1N hydrochloric acid per wash and then washed two times with 20 mL of water per wash. The organic layer was removed, mixed with 5 g of anhydrous sodium sulfate and evaporated to dryness. The resulting solid, 250 mg, was dissolved in 12.5 mL of anhydrous acetonitrile to form a 20 mg/mL cyclosporin C-hemisuccinate solution.

To 2 mL of the cyclosporin C-hemisuccinate solution formed above was added 14 mg of 2-fluoro-1-methylpyridinium toluene 4-sulfonate (Aldrich Chemicals) and 8 μ L of triethylamine. The resulting mixture was incubated at room temperature for one hour and 200 mg of bovine globulin in 50 mL of 0.1M sodium carbonate buffer (pH 9.5) was added, forming a cloudy solution. The solution was stirred on a magnetic stirrer plate at room temperature for approximately 18 hours. The solution was dialyzed against phosphate buffer saline (PBS, 10 mM sodium phosphate, 0.9% sodium chloride, pH 7.0) and diluted to 0.3 mg/mL bovine globulin with PBS, based on a starting bovine globulin concentration of 200 mg/52 mL.

Chromium dioxide particles were prepared as described in U.S. 4,661,408. To 250 mL of a chromium dioxide particle suspension (5% w/v of chromium dioxide particles in 10mM phosphate buffer) was added 250 mL of the cyclosporin C-hemisuccinate-globulin solution prepared above. The mixture was stirred for approximately 18 hours, washed eight times with 1L of wash buffer (10 mM TRIS, 150 mM sodium chloride, 0.05% Tween 20 and 0.3% chloroacetamide) per wash and two times with 1L of a 0.1% BSA solution in 10mM phosphate buffer per wash.

One hundred grams of Sephadex G-10 (Pharmacia Fine Chemicals) was mixed with 500 mL of 0.15M sodium phosphate buffer (pH 7.8) containing 5 g of PEI at room temperature for approximately 18 hours. Unbound PEI was removed by washing the mixture five times with 500 mL of distilled water per wash and two times with 500 mL of 0.15M sodium phosphate per wash.

Twenty-five mL of the cyclosporin C-hemisuccinate-globulin-chromium dioxide particle mixture prepared above was mixed thoroughly with 100 mL of PEI-Sephadex G-10 and 100 mL of 0.15M sodium phosphate buffer. The mixture was packed into aca® discrete clinical analyzer analytical columns (0.5 x 8 cm, 1.8 mL per column). The columns in turn were placed in the headers of aca® discrete clinical analyzer test packs containing 100 μ L of a 150 mg/mL solution of CPRG in water or, alternatively, 180 μ L of a 16 mg/mL solution of ReG in n-methylpyrrolidone which had been diluted 1:2 with water.

B. ENZYME-LINKED IMMUNOASSAY FOR MEASUREMENT OF CYCLOSPORIN A IN WHOLE BLOOD SAMPLES USING CPRG AND ReG AS β -D-GALACTOSIDASE SUBSTRATES

Whole blood cyclosporin A samples of various concentrations were prepared by adding cyclosporin A (Sandoz Ltd.) to whole blood to achieve cyclosporin A concentrations of 0, 100, 300, 500, and 1000 ng/mL.

These samples were divided into two sets, one for each of CPRG and ReG, and processed as follows. Red blood cells were lysed by adding 200 μ L of distilled water to 50 μ L of each sample. A 50- μ L aliquot of each lysate was then added to 50 μ L of β -D-galactosidase-labeled anti-cyclosporin antibody conjugate reagent (Sandoz Ltd.) and incubated for 20 minutes at room temperature. After incubation, each sample lysate-antibody mixture was automatically injected into an aca® discrete clinical analyzer analytical test pack and eluted through the column in the pack header. Each sample was followed by 2 mL of 0.15M sodium phosphate, pH 7.8. The column flow rate was 34 μ L/sec. The pack was then filled at needle position 2 (which bypasses the column) with an additional 2.9 mL of water. Substrate (either CPRG or ReG) was released from breaker/mixer II approximately 3.7 minutes later. Absorbance was measured at 577 nm, 29 and 46 sec after addition of substrate. The absorbance rates, expressed in mA/min, are shown in the Table for each cyclosporin A level in whole blood:

TABLE

Cyclosporin A (ng/mL whole blood)	Absorbance (mA/min at 577 nm)	
	CPRG	ReG
0	63	36
100	122	52
300	208	110
500	234	118
1000	262	141

As can be seen from the Table, absorbance rates (mA/min) were proportional to cyclosporin A levels in whole blood samples when CPRG and ReG were used as β -D-galactosidase substrates. Although CPRG exhibited greater sensitivity as evidenced by the higher absorbance rate per ng/mL of cyclosporin A, both substrates exhibited sensitivities suitable for precise and accurate measurement of cyclosporin A levels in whole blood samples using conventional spectrophotometers.

Claims

1. An enzyme-linked immunoassay for the measurement of cyclosporin A levels in whole blood samples comprising the steps of:
 - (a) lysing red blood cells in a sample of whole blood containing cyclosporin A;
 - (b) contacting the lysed whole blood sample with excess β -D-galactosidase-labeled anti-cyclosporin antibody to form a labeled antibody-cyclosporin A complex;
 - (c) separating unbound antibody from the complex by contacting the mixture formed in step (b) with a solid phase comprising cyclosporin immobilized on a solid support; and
 - (d) determining the amount of β -D-galactosidase label in the complex as a measure of cyclosporin A by adding a β -D-galactosidase substrate selected from chlorophenol red- β -D-galactopyranoside and resorufin- β -D-galactopyranoside.
2. An immunoassay according to Claim 1 wherein in step (c) the immobilized cyclosporin is cyclosporin C.
3. An immunoassay according to Claim 1 or 2 wherein in step (c) the solid phase is a beaded dextran containing an immobilized flocculating agent and trapped stabilized chromium dioxide particles having cyclosporin bound in their surfaces.
4. An immunoassay according to claim 3 wherein the flocculating agent is polyethyleneimine.



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	CLIN. CHEM., vol. 38, no. 1, 1987, pages 32-37; V. QUESNIAUX et al.: "Potential of monoclonal antibodies to improve therapeutic monitoring of cyclosporine" * Whole article * ---	1	G 01 N 33/68 G 01 N 33/58 G 01 N 33/548
A	EP-A-0 146 866 (BOEHRINGER MANNHEIM GmbH) * Abstract; claims * & US-A-4 668 622 (Cat. D) ---	1	
A	EP-A-0 156 347 (BOEHRINGER MANNHEIM GmbH) * Abstract; claims * & DE-A-3 411 574 (Cat. D) ---	1	
A	US-A-4 727 035 (W.C. MAHONEY) * Claims * -----	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			G 01 N
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 13-03-1990	Examiner HITCHEN C.E.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

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File: USPT

Mar 11, 2003

DOCUMENT-IDENTIFIER: US 6531139 B1

TITLE: Self-emulsifying formulation for lipophilic compounds

Brief Summary Text (64):

The emulsions or microemulsions generated from the present invention are conventional solutions comprising a hydrophilic phase and a lipophilic phase. Microemulsions are also characterized by their thermodynamic stability, optical transparency and small average droplet size, generally less than about 0.15 micron.

CLAIMS:

38. A pharmaceutical composition according to claim 37, wherein the microemulsion formed has an almost transparent or translucent appearance and the average particle (droplet) size of the emulsion is less than 150 nanometers (0.15 microns).

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DOCUMENT-IDENTIFIER: US 6531139 B1

TITLE: Self-emulsifying formulation for lipophilic compounds

Brief Summary Text (5):

However, like many other HIV protease inhibitors, these compounds are characteristically lipophilic and thus poorly water soluble. For example, the compound of formula I has an aqueous solubility about 1 .mu.g/ml in the buffer of pH 6.5 (close to the pH of the intestine), which is considered as extremely poor aqueous solubility and would be expected to provide very low oral bioavailability in the free acid form. It is well known that an active drug substance or therapeutic moiety administered by any route must possess some aqueous solubility for systemic absorption and therapeutic response. Poorly water soluble compounds often exhibit either incomplete or erratic absorption and thus produce a minimal response at desired dosage.

Brief Summary Text (7):

Recognizing the problems, the present invention is directed toward pharmaceutical compositions in a form of self-emulsifying formulations which provide high concentration and high oral bioavailability for pyranone compounds. In particular it has been discovered that the compositions of the present invention allow the preparation of self-emulsifying formulations containing a pyranone inhibitor of retroviral protease in an exceedingly high concentration up to about 400 mg/g to permit convenient oral administration while at the same time achieving improved bioavailability, which is at least two fold higher than the aqueous suspension of the free acid.

Brief Summary Text (14):

UK Patent, GB 2,257,359B discloses pharmaceutical compositions suitable for oral administration comprising a cyclosporin, 1,2-propylene glycol, a mixed mono-, di-, and tri-glyceride and a hydrophilic surfactant.

Brief Summary Text (18):

A further object of the present invention is to provide a pharmaceutical composition containing a high drug load of a lipophilic, pharmaceutically active agent for convenient administration.

Brief Summary Text (64):

The emulsions or microemulsions generated from the present invention are conventional solutions comprising a hydrophilic phase and a lipophilic phase. Microemulsions are also characterized by their thermodynamic stability, optical transparency and small average droplet size, generally less than about 0.15 micron.

Brief Summary Text (70):

The amount of active ingredient in the composition may vary or be adjusted widely depending on the intended route of administration, the potency of the particular active ingredient being used, the severity of the illness and the required concentration. If desired, however, a lipophilic pharmaceutically active agent can be present in the self-emulsifying formulation vehicle of the present invention in an amount up to about 400 mg/g with excellent dispersability and high oral bioavailability in vivo typically reaching 70-84% in rats.

Detailed Description Text (55):

(i) Sprague-Dawley male rats were selected for the in vivo oral bioavailability study. Each rat was prepared by the surgical implantation of an indwelling cannula in the superior vena cava. Each rat, in the weight range of 300-400 g, was fasted overnight prior to dosing. Each formulation was orally administered to a group of rats (n=3) at a 20 mg/kg dose. The formulations with high concentration of

the compound of formula I (typically 200-300 mg/g) was diluted by 100-fold with water and injected directly into the rat's stomach using oral gavage. Serial blood samples of 0.25 ml were obtained from the indwelling cannula at 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing. These blood samples were analyzed using a HPLC assay specific for the testing compounds. Drug concentrations in the blood of the test rats are plotted against the time after the drug is administered through an intravenous (i.v.) or oral route and the AUCs (the Area Under the Plasma Concentration-Time Curve) are integrated using the trapezoidal rule to calculate the absolute bioavailability as shown in Table 1. ##EQU1##

Detailed Description Text (56):

(ii) Male Beagle dogs were also selected for the in vivo oral bioavailability study. Each dog, in the weight range of 13.5-17.5 kg, was fasted overnight prior to dosing. Each formulation was orally administered to a group of dogs (n=4) at a 20 mg/kg dose. The formulation of high concentration of the compound of formula I (300 mg/g) was encapsulated in gelatin capsules and administered. Serial blood samples of 2 ml were obtained from the jugular vein at 20, 40 minutes and 1, 2, 4, 6, 8, 12, and 24 hours after dosing. These blood samples were analyzed using a HPLC assay specific for the compound of formula I. The blood concentrations of the compound of formula I are plotted against the time and the AUCs are obtained to calculate the absolute bioavailability. The results are shown in Table 2.

Detailed Description Text (57):

(iii) Ten healthy volunteers were orally administered with eight 150 mg (1200 mg single dose) disodium salt of compound of the formula I encapsulated in hard gelatin capsules as reference. Weeks later, the same group were orally administered with four 300 mg (1200 mg single dose) compound of the formula I in a formulation as exhibited in Example 15. Serial blood samples of two group volunteers were obtained at 30 minutes and 1, 2, 4, 6, 8, 12, and 24 hours after dosing. These blood samples were analyzed using a HPLC assay specific for the compound of formula I. The blood concentrations of the compound of formula I are plotted against the time and the AUCs are obtained to calculate the absolute bioavailability. The results are shown in Table 3.

CLAIMS:

38. A pharmaceutical composition according to claim 37, wherein the microemulsion formed has an almost transparent or translucent appearance and the average particle (droplet) size of the emulsion is less than 150 nanometers (0.15 microns).

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KMIC	Draw Des				
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Display Format:

17875137 PMID: 15542182

Risk factors for acellular and whole - cell pertussis vaccine failure in Senegalese children.

Lacombe Karine; Yam Abdoulaye; Simondon Kirsten; Pinchinat Sybil; Simondon Francois

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Vaccine (Netherlands). Dec 16 2004, 23 (5) p623-8, ISSN 0264-410X
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Subfile: INDEX MEDICUS

Although use of acellular pertussis vaccine was associated with a higher rate of vaccine **failure** than that of **whole** -cell vaccine in the Senegal Pertussis Trial conducted in 1990-1994 on 4189 children, risk factors for vaccine **failure** regarding exposure and susceptibility to pertussis have not been studied so far. Pertussis occurred in 346 vaccinated children. Three factors were found to be associated with vaccine **failure**, independently of the vaccine type, namely the degree of exposure, birth rank, and time since weaning. In the **whole** -cell vaccine group, the risk of **failure** increased with birth rank [RR = 2.95 (1.51-5.75)] and was higher in non stunted children [RR = 1.43 (1.05-1.94)]. In the acellular vaccine group, the risk of **failure** increased with age at exposure to B. pertussis [RR = 2.24 (1.21-4.12) after 18 months of age] and the degree of exposure [RR = 2.14 (1.17-3.93) when the child shared the hut of an index case]. These results highlight the influence of environmental factors on the success of pertussis vaccination. However, they do not explain the shorter duration of protection provided by the acellular vaccine compared to the **whole** -cell vaccine which persist after controlling and thus might be related to the nature of the vaccine.

Tags: Female; Male; Research Support, Non-U.S. Gov't

Descriptors: *Bordetella pertussis--immunology--IM; *Pertussis Vaccine--immunology--IM; *Whooping Cough--prevention and control--PC; Birth Order; Child, Preschool; Cohort Studies; Follow-Up Studies; Humans; Infant; Infant, Newborn; Pertussis Vaccine--administration and dosage--AD; Risk Factors; Senegal; Time Factors; Treatment **Failure**; Vaccines, Acellular--administration and dosage--AD; Vaccines, Acellular--immunology--IM; Weaning

CAS Registry No.: 0 (Pertussis Vaccine); 0 (Vaccines, Acellular)

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10319443 PMID: 8411101

Whole inactivated SIV vaccine grown on human cells fails to protect against homologous SIV grown on simian cells.

Putkonen P; Nilsson C; Hild K; Benthin R; Cranage M; Aubertin A M; Biberfeld G

Department of Immunology, National Bacteriological Laboratory, Stockholm, Sweden.

Journal of medical primatology (DENMARK) Feb-May 1993, 22 (2-3)
p100-3, ISSN 0047-2565 Journal Code: 0320626

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Several groups have reported protection against experimental SIV infection in macaques immunized with a **whole** inactivated virus vaccine. The aim of the current study was to investigate whether five macaques vaccinated with **whole** inactivated SIV and previously shown to be protected against challenge with two divergent strains of SIV grown on human cells could resist challenge with a subsequent homologous SIV grown on macaque cells. We show here that this same vaccine did not protect when the challenge virus was grown on primary cells of monkey origin.

Tags: Research Support, Non-U.S. Gov't

Descriptors: *SIV--immunology--IM; *Simian Acquired Immunodeficiency Syndrome--prevention and control--PC; *Viral Fusion Proteins; *Viral Vaccines--pharmacology--PD; AIDS Vaccines--isolation and purification--IP; Animals; Cell Line; Disease Models, Animal; Gene Products, env--immunology--IM; Humans; Macaca fascicularis; Retroviridae Proteins, Oncogenic--immunology--IM; SIV--growth and development--GD; Simian Acquired Immunodeficiency Syndrome--immunology--IM; Species Specificity; Vaccines, Inactivated--isolation and purification--IP; Vaccines, Inactivated--pharmacology--PD; Viral Vaccines--isolation and purification--IP; Virus Cultivation--methods--MT

CAS Registry No.: 0 (AIDS Vaccines); 0 (Gene Products, env); 0 (Retroviridae Proteins, Oncogenic); 0 (Vaccines, Inactivated); 0 (Viral Fusion Proteins); 0 (Viral Vaccines); 0 (simian immunodeficiency virus transmembrane protein)

Record Date Created: 19931123

Record Date Completed: 19931123

5/9/3 (Item 3 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

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08952436 PMID: 2157886

Inactivated simian immunodeficiency virus vaccine failed to protect rhesus macaques from intravenous or genital mucosal infection but delayed disease in intravenously exposed animals.

Sutjipto S; Pedersen N C; Miller C J; Gardner M B; Hanson C V; Gettie A; Jennings M; Higgins J; Marx P A

California Primate Research Center, University of California, Davis 95616.

Journal of virology (UNITED STATES) May 1990, 64 (5) p2290-7, ISSN 0022-538X Journal Code: 0113724

Contract/Grant No.: AI20573; AI; NIAID; AI62559; AI; NIAID; RR00169; RR; NCRR; +

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; AIDS/HIV

Eight rhesus macaques were immunized four times over a period of 8 months with a psoralen-UV-light-inactivated **whole** simian immunodeficiency virus

vaccine adjuvanted with threonyl muramyl dipeptide. Eight unvaccinated control animals received adjuvant alone. Only the vaccinated animals made antibodies before challenge exposure to the viral core and envelope as determined by Western blotting (immunoblotting) and virus-neutralizing antibodies. Ten days after the final immunization, one-half of the vaccinated and nonvaccinated monkeys were challenged exposed intravenously (i.v.) and one-half were challenge exposed via the genital mucosa with virulent simian immunodeficiency virus. All of the nonvaccinated control monkeys became persistently infected. In spite of preexisting neutralizing antibodies and an anamnestic antibody response, all of the immunized monkeys also became persistently infected. However, there was evidence that the clinical course in immunized i.v. infected animals was delayed. All four mock-vaccinated i.v. challenge-exposed animals died with disease from 3 to 9 months postchallenge. In contrast, only one of four vaccinated i.v. challenge-exposed monkeys had died by 11 months postchallenge.

Tags: Female; Male; Research Support, U.S. Gov't, Non-P.H.S.; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Genital Diseases, Female--microbiology--MI; *Genital Diseases, Male--microbiology--MI; *Retroviridae Infections--prevention and control--PC; *SIV--immunology--IM; *Vaccines, Attenuated--administration and dosage--AD; *Viral Vaccines--administration and dosage--AD; Adjuvants, Immunologic--administration and dosage--AD; Animals; Antibody Formation; Cell Line; Genital Diseases, Female--immunology--IM; Genital Diseases, Female--prevention and control--PC; Genital Diseases, Male--immunology--IM; Genital Diseases, Male--prevention and control--PC; Humans; Immunization Schedule; Macaca mulatta; Mucous Membrane--microbiology--MI; Neutralization Tests; Psoralens; Retroviridae Infections--immunology--IM; Retroviridae Infections--transmission--TM; SIV--isolation and purification--IP; SIV--pathogenicity--PY; Ultraviolet Rays; Virulence

CAS Registry No.: 0 (Adjuvants, Immunologic); 0 (Psoralens); 0 (Vaccines, Attenuated); 0 (Viral Vaccines)

Record Date Created: 19900524

Record Date Completed: 19900524

10784160 PMID: 7986589

High-titer immune responses elicited by recombinant vaccinia virus priming and particle boosting are ineffective in preventing virulent SIV infection.

Daniel M D; Mazzara G P; Simon M A; Sehgal P K; Kodama T; Panicali D L; Desrosiers R C

New England Regional Primate Research Center, Harvard Medical School, Southborough, Massachusetts 01772-9102.

AIDS research and human retroviruses (UNITED STATES) Jul 1994, 10 (7)

p839-51, ISSN 0889-2229 Journal Code: 8709376

Contract/Grant No.: AI26507; AI; NIAID; RR00168; RR; NCRR

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS; AIDS/HIV

Eighteen rhesus monkeys were vaccinated with recombinant vaccinia viruses expressing SIVmac antigens in 3 separate rounds of experiments. Twelve of the monkeys were primed with a trivalent vaccinia virus recombinant expressing Gag, Pol, and Env polypeptides that can assemble into SIV pseudovirion particles and boosted with SIV particles in adjuvant. Four of the monkeys were primed with different vaccinia virus recombinants expressing env or gag+env followed by SIV particle boosts; two received vaccinia virus recombinants alone (env or env+gag). Despite the induction of vigorous immune responses, 17 of 18 rhesus monkeys became infected on challenge with a low dose of virulent SIVmac. The single protected animal was one of three challenged with homologous cloned SIV exactly matched to the clone used for construction of trivalent vaccinia virus recombinant and particles. Vaccination may have diminished SIV burdens and rates of CD4+ cell declines in some of the animals, but vaccinated/challenge/infected animals eventually developed fatal disease similar to control animals. These results highlight the extreme difficulty in achieving vaccine protection against virulent SIVmac infection even under idealized laboratory conditions.

Tags: Research Support, U.S. Gov't, P.H.S.

Descriptors: *SAIDS Vaccines--administration and dosage--AD; *SIV --pathogenicity--PY; *Simian Acquired Immunodeficiency Syndrome--prevention and control--PC; Animals; Antibody Formation; Blotting, Western; CD4-Positive T-Lymphocytes--pathology--PA; Immunization, Secondary; Macaca mulatta; SIV--immunology--IM; Simian Acquired Immunodeficiency Syndrome --immunology--IM; Trachea--pathology--PA; Trachea--ultrastructure--UL; Vaccination; Virulence

CAS Registry No.: 0 (SAIDS Vaccines)

Record Date Created: 19950109

Record Date Completed: 19950109

6/9/3 (Item 3 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

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08891509 PMID: 2304207

Ineffectiveness and comparative pathogenicity of attenuated rabies virus vaccines for the striped skunk (*Mephitis mephitis*).

Rupprecht C E; Charlton K M; Artois M; Casey G A; Webster W A; Campbell J B; Lawson K F; Schneider L G

Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania 19104.

Journal of wildlife diseases (UNITED STATES) Jan 1990, 26 (1)
p99-102, ISSN 0090-3558 Journal Code: 0244160

Contract/Grant No.: AI-09206-16; AI; NIAID

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Three attenuated rabies virus vaccines (SAD-B19, ERA/BHK-21, AZA 2) were compared for efficacy and safety in the striped skunk (*Mephitis mephitis*) by the oral and intranasal routes. The SAD-B19 and ERA/BHK-21 vaccines were given orally; all three vaccines were given intranasally. Oral administration of SAD-B19 and ERA/BHK-21 vaccines induced neither seroconversion nor significant protection against rabies challenge. One skunk which consumed a SAD-B19 vaccine-laden bait succumbed to vaccine-induced rabies. Intranasal instillation of the three vaccines resulted in the deaths of two of six (AZA 2), three of six (ERA/BHK-21) and six of six (SAD-B19) skunks.

Tags: Comparative Study; Female; Male; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Carnivora; *Mephitidae; *Rabies--veterinary--VE; *Rabies Vaccines--adverse effects--AE; Administration, Intranasal; Administration, Oral; Animals; Antibodies, Viral--biosynthesis--BI; Rabies--prevention and control--PC; Rabies Vaccines--administration and dosage--AD; Rabies Vaccines--immunology--IM; Rabies virus--immunology--IM; Vaccines, Attenuated--administration and dosage--AD; Vaccines, Attenuated--adverse effects--AE; Vaccines, Attenuated--immunology--IM

CAS Registry No.: 0 (Antibodies, Viral); 0 (Rabies Vaccines); 0 (Vaccines, Attenuated)

Record Date Created: 19900327

Record Date Completed: 19900327

6/9/5 (Item 5 from file: 155)

DIALOG(R) File 155:MEDLINE(R)

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05482304 PMID: 218709

The calf reo-like virus (rotavirus) vaccine : an ineffective immunization agent for rotaviral diarrhea of piglets.

Lecce J G; King M W

Canadian journal of comparative medicine. Revue canadienne de medecine comparee (CANADA) Jan 1979, 43 (1) p90-3, ISSN 0008-4050

Journal Code: 0151747

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Rotavirus, in a commercially available calf vaccine, did not replicate in newborn colostrum-free piglets inoculated orally with one half of a calf dose. Gross and microscopic examination of these vaccinated piglets revealed no lesions consistent with rotaviral infection and vaccinated piglets were susceptible to challenge by porcine rotavirus. Challenged piglets vomited, had diarrhea and became severely dehydrated. Rotavirus was visualized in their gut fluid. Villi in the small intestines were shortened, blunted and fused. Rotaviral antigens were seen in enterocytes.

Tags: Research Support, U.S. Gov't, P.H.S.
Descriptors: *Diarrhea--veterinary--VE; *RNA Viruses--immunology--IM;
*Rotavirus--immunology--IM; *Swine Diseases--prevention and control--PC;
*Viral Vaccines--immunology--IM; Animals; Cattle; Diarrhea--prevention and
control--PC; Intestine, Small--pathology--PA; Swine; Vaccines, Attenuated
--immunology--IM; Virus Diseases--immunology--IM; Virus Diseases
--pathology--PA
CAS Registry No.: 0 (Vaccines, Attenuated); 0 (Viral Vaccines)
Record Date Created: 19790611
Record Date Completed: 19790611

6/9/6 (Item 1 from file: 5)
DIALOG(R) File 5: Biosis Previews(R)
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0012111387 BIOSIS NO.: 199900371047
**Influenza vaccination is ineffective in the first 2 years after stem
cell transplant**
AUTHOR: Gandhi M K (Reprint); Egner W; Inman I (Reprint); Craig J I O
(Reprint); Marcus R E (Reprint)
AUTHOR ADDRESS: Department of Haematology, Addenbrooke's Hospital,
Cambridge, UK**UK
JOURNAL: British Journal of Haematology 105 (SUPPL. 1): p31 April, 1999
1999
MEDIUM: print
CONFERENCE/MEETING: Annual Scientific Meeting of the British Society for
Haematology Brighton, England, UK April 12-15, 1999; 19990412
SPONSOR: British Society for Haematology
ISSN: 0007-1048
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English
DESCRIPTORS:
MAJOR CONCEPTS: Clinical Immunology--Human Medicine, Medical Sciences;
Infection; Pharmacology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata,
Animalia; Orthomyxoviridae--Negative Sense ssRNA Viruses, Viruses,
Microorganisms
ORGANISMS: human (Hominidae)--patient; influenza virus (Orthomyxoviridae)
--pathogen
COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates;
Vertebrates; Microorganisms; Negative Sense Single-Stranded RNA Viruses
; Viruses
DISEASES: influenza--respiratory system disease, viral disease
MESH TERMS: Influenza (MeSH)
CHEMICALS & BIOCHEMICALS: influenza vaccine--vaccine
METHODS & EQUIPMENT: influenza vaccination--immunization method,
ineffective ; stem cell transplant--allogeneic, therapeutic method,
autologous, transplantation method
MISCELLANEOUS TERMS: humoral immunity; Meeting Abstract; Meeting
Abstract
CONCEPT CODES:
34502 Immunology - General and methods °
10060 Biochemistry studies - General
11107 Anatomy and Histology - Regeneration and transplantation
12512 Pathology - Therapy
36006 Medical and clinical microbiology - Virology
22002 Pharmacology - General

15001 Blood - General and methods

00520 General biology - Symposia, transactions and proceedings

BIOSYSTEMATIC CODES:

86215 Hominidae

03505 Orthomyxoviridae

? logoff hold

DOCUMENT-IDENTIFIER: US 4873090 A

TITLE: Non-adjuvenated vaccine

Brief Summary Text (8):

The enteric vaccine may be in the form of tablets, especially enteric coated tablets, granules, capsules or dragees for oral administration, or provided e.g. as suppositories for rectal administration. The dosage unit form may contain from approximately 10.sup.9 bacteria to approximately 10.sup.13 bacteria, preferably from approximately 10.sup.10 bacteria to approximately 10.sup.12 bacteria, together with suitable carriers of organic or inorganic nature.

Brief Summary Text (14):

The invention is applicable to patients having long term diseases of mucosal sites, e.g. of the respiratory tract, eye, urogenital system and the gut. These mucosal sites form part of a common mucosal system linked by an intermucosal cell traffic. Certain infections are restricted to mucosal sites and are thus not susceptible to antibodies in the bloodstream. In the present invention the antigen is administered enterally, i.e. to the gut, and activated cells then circulate through the blood to lodge at distant mucosal sites, where they secrete their antibody on the mucosal surface or act directly on it.

Detailed Description Paragraph Table (4):

_____ cellulose acetate phthalate 12 g propylene glycol 3 g
Tween 80 .RTM. 1 g alcohol abs. 40 ml iron oxide red pigment 0.30 g iron oxide yellow pigment 1.20 g
acetone to 100 ml _____

WEST Search History

DATE: Wednesday, June 22, 2005

Hide?	<u>Set</u> <u>Name</u>	<u>Query</u>	<u>Hit</u> <u>Count</u>
	<i>DB=USPT; PLUR=YES; OP=AND</i>		
<input type="checkbox"/>	L1	3551554.pn.	1
<input type="checkbox"/>	L2	L1 and suppositor\$	0
<input type="checkbox"/>	L3	L1 and suppositor\$.clm.	0
	<i>DB=USOC; PLUR=YES; OP=AND</i>		
<input type="checkbox"/>	L4	3551554.pn.	1
<input type="checkbox"/>	L5	L4 and suppositor\$.clm.	0
<input type="checkbox"/>	L6	L4 and suppository.clm.	0
	<i>DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND</i>		
<input type="checkbox"/>	L7	3551554.pn.	4
<input type="checkbox"/>	L8	L7 and suppository.clm.	0
<input type="checkbox"/>	L9	suppositor\$ near5 (cream or lotion or jelly or vehicle or depot or base or foam)	19385
<input type="checkbox"/>	L10	penile or urogenital\$ or genitourinary or genitor-urinary or uro-genital\$ or urino-genital or vaginal\$ or urinogenital\$	46748
<input type="checkbox"/>	L11	poly near sorbate	102
<input type="checkbox"/>	L12	poly-sorbate\$	21
<input type="checkbox"/>	L13	polysorbate\$	20267
<input type="checkbox"/>	L14	tween\$	437465
<input type="checkbox"/>	L15	tween	429171
<input type="checkbox"/>	L16	L15 or l14 or l13 or l12 or l11	450244
<input type="checkbox"/>	L17	polyethylene near glycol	200811
<input type="checkbox"/>	L18	poly near ethylene near glycol	13322
<input type="checkbox"/>	L19	poly-ethylene near glycol	1106
<input type="checkbox"/>	L20	poly-ethylene-glycol	63
<input type="checkbox"/>	L21	poly-ethylene-glycol\$	74
<input type="checkbox"/>	L22	peg	111522
<input type="checkbox"/>	L23	peg\$	133828
<input type="checkbox"/>	L24	peglyate	0
<input type="checkbox"/>	L25	pegylat\$	5179
<input type="checkbox"/>	L26	L25 or l24 or l23 or l22 or l21 or l20 or l19 or l18 or l17	296247
<input type="checkbox"/>	L27	l9 and l10 and l16 and l26	2116

<input type="checkbox"/>	L28	l9 same l10 same l16 same l26	28
<input type="checkbox"/>	L29	l9.ti,ab,clm. and l10.ti,ab,clm. and l16.ti,ab,clm. and l26.ti,ab,clm. not l28	8
<input type="checkbox"/>	L30	(HERTELENDY.in. or HOWELL.in. or THOMAS.in. or WEINER.in.) and l9	730
<input type="checkbox"/>	L31	L30 and l10	322
<input type="checkbox"/>	L32	polyoxyethlenesorbitan or poly-oxy-ethylene-sorbitan or polyoxy-ethylenesorbitan or polyoxy-ehtylene-sorbitan	27
<input type="checkbox"/>	L33	(L32 or l16) and l30	252
<input type="checkbox"/>	L34	L33 and l26	192
<input type="checkbox"/>	L35	(3880991 4606919 4820698 4939284 5057520 5057523 5270344 5364879)! [pn]	14
<input type="checkbox"/>	L36	l9 near10 l10	1231
<input type="checkbox"/>	L37	L36 and l26.clm. and (l16 or l32).clm.	8
<input type="checkbox"/>	L38	L36 and (l26 same (l16 or l32)) not l37	185
<input type="checkbox"/>	L39	arabinofuranosyl or iodouracil or FIAU or fialuridine	5948
<input type="checkbox"/>	L40	L39 near2 (anti or antibodies or antibody or immune or humoral or cellular or immunoglobulin or polyclonal or antiserum or antisera or anti-sera or monoclonal or mab or moab)	15

END OF SEARCH HISTORY